

Examining the Link between EZH2 and Chromosomal Instability in Metastatic Breast Cancer

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Abstract: Chromosomal instability (CIN) is a hallmark of triple-negative breast cancer (TNBC) and it is associated with metastasis, immune evasion, and therapeutic resistance. Despite its widespread prevalence, there are no therapies that have been shown to directly suppress CIN in cancer. We made the unexpected discovery that a master epigenetic regulator EZH2 often overexpressed in metastatic breast cancer promotes CIN. EZH2 is part of the Polycomb repressive complex 2 (PRC2) and it generates heterochromatin formation through the trimethylation of lysine 27 of Histone H3 (H3K27me3). Interestingly, depletion of EZH2 or its pharmacologic inhibition leads to suppression of CIN and metastasis only in basal and stem-like breast cancer cells suggesting that its aberrant activation impacts mitotic chromosome segregation in a context-dependent manner. In this proposal, we will aim to mechanistically understand how EZH2 promotes CIN first by asking whether EZH2 activation disrupts proper mitotic spindle formation through dysregulation of EZH2 target genes (Aim 1). We will next examine the impact of aberrant EZH2 activity on centromere organization and ask whether EZH2 disrupts the centromere in a manner that interferes with the assembly of the kinetochore – the site of attachment of chromosomes to spindle microtubules (Aim 2). Finally, we will ask whether EZH2 enables tolerance to CIN by promoting a basal-like phenotype that is more tolerant to genomic abnormalities (Aim 3). Our work addresses a fundamental relationship between two hallmarks of advanced breast cancer and if successful would lead to the development of the first ever CIN suppressive therapeutic strategy in human cancer.